Effect of Alterations in Vasomotor Tone on Pressure-Flow Relationships in the Totally Perfused Dog

By Raymond C. Read, M.D., F.R.C.S., Hiroshi Kuida, M.D. and John A. Johnson, Ph.D.

The technic of total body perfusion with a pump oxygenator system has been used to extend pressure flow studies to the circulation as a whole. The effect of alterations in vasomotor tone on both total peripheral resistance and pressure flow relationships has been investigated by surgical ablation of the central nervous system or administration of vasoactive drugs. Certain aspects of the results obtained are discussed in relation to the concept of critical closing pressures.

Previous studies of pressure-flow relationships have been largely restricted to regional vascular beds. The development of technics for total body perfusion has provided an opportunity to extend these investigations to the circulation as a whole. In an earlier study it was found that under the conditions of total body perfusion an approximately linear relationship existed between pressure and flow with an extrapolated intercept on the pressure axis. This work suffered from the fact that the results were derived from pooled data obtained in a large number of dogs in each of which only a few changes in flow were made.

The purpose of the present study was to investigate, in individual animals, pressure-flow relationships over a wide range of flow rates. Particular emphasis was placed on obtaining data at low flows in order to evaluate the concept of critical closing pressure. The effect of changes in vasomotor tone on total peripheral resistance and pressure-flow curves was studied by the use of ganglionic blocking drugs and surgical destruction of the central nervous system.

METHODS

Thirty-three dogs whose weights ranged from 4.9 to 12.2 Kg. (average 8.1 Kg.) were lightly anesthetized with pentothal sodium and succinylcholine. Total body perfusion was carried out by previously described methods. Flow was maintained constant in 21 experiments in which the effects of changes in vasomotor tone on calculated total peripheral resistance were studied. In the remaining 12 animals complete pressure-flow curves were obtained, necessitating minor modifications in the perfusion technic to permit rapid serial changes in flow rate. In this latter group a special effort was made to achieve control perfusion rates approximating physiologic cardiac output. The levels obtained were variable and depended upon animal size, capacity of the oxygenator, and maintenance of an approximately normal venous pressure.

The output of the arterial pump was not altered throughout the experiments after the control rate was established, and was measured at the end of each study with a graduated cylinder and stopwatch. Previous work has shown that the output of the sigma motor pump used is independent of pressures encountered in these studies. In the pressure-flow studies, flow into the dog was altered by diverting varying fractions of the total pump output through a shunt placed proximal to the arterial cannula. Blood flow through the shunt was controlled by means of a screw clamp which was adjusted to impose varying fixed resistances. Shunt flow was measured in a calibrated constant cross sectional reservoir with a pressure gage. Flow into the animal was derived by subtracting the shunt flow from the total pump output.

Each different flow rate was maintained for 60 to 90 sec. after which the animal was returned to the control level for a period of 2 to 5 min. to allow recovery. Flow into the animal was constant as judged by the fact that shunt flow measurements at the beginning and end of each 60 to 90 sec. period agreed within 1 per cent. The reason that shunt flow remained constant in spite of changes in the animals blood pressure is that the arterial cannula used in these studies represented the major resistance to pump output. Periods of reduced flow were restricted to 90 sec. or less to obviate changes resulting from ischemia. Zero flow was produced by clamping the arterial inflow cannula; the total output of the pump was thus diverted through the shunt and
measurements of this quantity made during the experiment agreed well with those determined at the end of the study using the graduate cylinder.

Venous return in the early studies was drained through a single caval catheter as described previously. This technical had a maximal drainage capacity of approximately 900 ml./min. and a minor modification was made in later experiments to permit higher flow rates. This consisted of separate cannulation of the superior and inferior vena cavae which were then allowed to drain into a reservoir connected to the venous pump. Venae caval pressures were equalized at the desired level by adjusting the hydrostatic level of drainage for each cannula.

Ventricular fibrillation was electrically induced in all preparations to obviate any residual cardiac output. Coronary venous return into the right heart was siphoned through a cannula tied into the main pulmonary artery. Bronchial artery flow returning to the left heart was also drained by incision of the left atrium. Aortic and inferior vena caval pressures were measured continuously with Statham strain gages through polyethylene catheters inserted via the femoral vessels, and recorded along with the pressure-time slope of the reservoir used to measure shunt flow on a Sanborn polyviso.

Mean* pressure-time slope of the reservoir used to measure shunt flow on a Sanborn polyviso was obtained. This usually required massive doses of the drug (10 to 100 mg.) in animals previously treated with ganglionic blocking agents.

**Results**

Control flow rates for the total series of 33 dogs are shown in Table 1, along with their total peripheral resistances before and after changes in vasomotor tone. Decapitation and pithing of the spinal cord or administration of hexamethonium, Arfonad* or Aramine† pithing was accomplished by first decapitating the animal and then curetting out the spinal cord. Hexamethonium was administered in divided doses until no further drop in blood pressure could be elicited, (approximately 50 to 75 mg.). Arfonad was given in a similar fashion (50 to 100 mg.). Aramine was injected until a blood pressure above control values was obtained. This usually required massive doses of the drug (10 to 100 mg.) in animals previously treated with ganglionic blocking agents.

was subsequently injected in 5 of these animals without a significant change in total peripheral resistance. In 6 dogs that received hexamethonium without prior surgical denervation the decrease in resistances was similar to the pithed group and averaged 39 per cent of control levels. Arfonad was administered to 9 dogs after previous denervation with either hexa-

### Table 1.—Total Peripheral Resistance Data

<table>
<thead>
<tr>
<th>Dog number</th>
<th>Weight (Kg.)</th>
<th>Control flow rate (ml./min.)/Kg.</th>
<th>T.P.R. at control flow rate—mm. Hg./ml./min./Kg.</th>
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<tbody>
<tr>
<td></td>
<td></td>
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<td>Intact</td>
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</table>

Animals in which complete pressure-flow studies were carried out:

<table>
<thead>
<tr>
<th>Dog number</th>
<th>Weight (Kg.)</th>
<th>Control flow rate (ml./min.)/Kg.</th>
<th>T.P.R. at control flow rate—mm. Hg./ml./min./Kg.</th>
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<td>1.10</td>
</tr>
<tr>
<td>50</td>
<td>6.3</td>
<td>101</td>
<td>1.30</td>
</tr>
</tbody>
</table>

Mean* | 5.8 | 90(33) | 1.53 | 0.92 | 0.79 | 0.57 | 2.33 |

* Numbers in parentheses indicate the number of observations from which mean values were derived.

* Trimethaphan camphorsulfonate (50 mg./ml.) Hoffman-LaRoche, Inc., Nutley, N. J.
† Metaraminol (10 mg./ml.) Sharp and Dohme, West Point, Pa.
vasomotor tone and pressure-flow relationships

Fig. 1. Relationship between A-V pressure difference and flow in 6 dogs. Group of points at the upper limit of each curve, pressures at control flows existing between each change in flow rate.

methonium or pithing or a combination of these two procedures. Eight animals received Arfonad without previous treatment. The change in resistance relative to control values was practically identical in the groups averaging 60 and 65 per cent respectively. Thus, Arfonad consistently produced a decrement of 25 per cent of the resistance in the preparations previously denervated surgically or by ganglionic blockade. Aramine was given to a total of 7 animals, only 2 of which had not previously been subjected to vasodilatory influences. Their resistances increased by an average of 80 per cent above control levels as a result of the administration of this drug.

Pressure-Flow Curves. The control flow rates in the 12 dogs in which complete pressure-flow studies were performed ranged from 82 to 170 ml./min./Kg., thus encompassing the normal range of resting cardiac output in the dog (table 1). Studies were made in 11 "intact preparations." Pressure-flow curves were obtained under conditions of altered vasomotor tone in 6 dogs. The pressure-flow curves were unaffected by whether flow was changed in step-wise decrements or graduated increments, control flow being re-established between each change.

Eleven individual curves were obtained in which blood pressure values were taken at 15 sec. after establishing a given flow rate and 6 studies at 60 sec. (fig. 1). A finite pressure at zero flow was a uniform finding as was a convexity to the pressure axis at flow rates below 20 ml./min./Kg. The remaining portion of the curves could be characterized into three types. The animals with the highest control resistances had curves which showed curvilinearity with a convexity to the pressure axis at higher flows. Two animals with low control resistances showed sigmoid curves. Curves between these two extremes were essentially linear beyond the initial convexity.

Influence of Pithing. The pressure-flow curves in 2 animals in which decapitation and subsequent pithing of the spinal cord were performed are shown in figure 2. Again, a positive pressure intercept at zero flow was found with a curvilinear origin. The remaining portions of the curves were essentially linear. In these animals the resistance was reduced from 1.34 in the "intact" perfused state to 0.64 mm. Hg/ml./min./Kg. after pithing.

Effect of Hexamethonium. This drug was administered to 6 animals. The drop in resistance resulting from the use of this agent was similar in magnitude to that associated with pithing of the spinal cord as demonstrated in both figure 3 and table 1. Pressure-flow curves in the 6 animals are shown in figure 2 and were very similar to those obtained in the pithed preparation.

Effect of Arfonad. This drug was given subsequent to the administration of hexamethonium in 4 animals. In each instance there was a further significant fall in resistance. The average vascular resistance after hexamethonium treatment in these dogs was 0.82 P.R.U., decreasing to 0.48 P.R.U. after the administration of Arfonad (fig. 2). In spite of the low vascular resistance a positive pressure intercept was still found. In other respects the shape of the curves was similar to those seen after pithing or the administration of hexamethonium.

Effect of Aramine. Three animals received Aramine in doses sufficient to raise the blood pressure above control levels. In 2 dogs this drug was given after the previous administration of Arfonad. In the other experiment it was given after hexamethonium treatment. The vascular resistances in these 3 animals were significantly higher than control levels and in keeping with the previous finding in intact
animals with a high resistance showed a curvilinear relationship throughout the entire range of flows (fig. 2). In spite of the increase in resistance the pressure intercept was not significantly different to that found in the control studies.

As can be seen from table 1, 2 dogs had pressure-flow relationships determined serially in the intact state and after subsequent administration consecutively of hexamethonium, Arfonad, and Aramine. The alterations in the pressure-flow curve brought about by these procedures in a single animal are shown in figure 4. The effect of reduced flow on total vascular resistance is shown in figure 5. The difference between the 15 and 50 sec. arteriovenous pressure difference at constant flow is greatest in the intact curve and persists to a lesser degree after treatment with hexamethonium. Arfonad, however, obliterates this effect except at zero or very low flows. When Aramine was administered after prior treatment with Arfonad the change in pressure with duration of reduced flow was less than that seen in the intact preparation despite the considerably

Fig. 2. Pressure-flow relationships under varying conditions of vasomotor tone. Symbols as in figure 1.

Fig. 3. Pressure flow relationship existing in an animal after pithing (closed circles) and after hexamethonium (open circles).
FIG. 4. Pressure flow curves in a single dog before and after consecutive administration of hexamethonium, Arfonad, and Aramine. Closed circles, blood pressure values 15 sec.; open circles, 60 sec. after each change in flow. Note increasing convexity to pressure axis with elevation of vasomotor tone.

FIG. 5. Total peripheral resistance from data in figure 4 plotted against flow.

higher absolute level of pressure. The magnitude of the intercept on the pressure axis at zero flow was roughly correlated with the level of vasomotor tone.

DISCUSSION

The decrease in total peripheral resistance by about a third brought about by hexamethonium was similar to that seen after surgical ablation of the central nervous system, confirming the pure ganglion-blocking effects of this drug. The further fall in vascular resistance which followed treatment with Arfonad suggests that the vasodilatation brought about by this agent depends upon an additional mechanism. Bronchospasm and both pulmonary and hepatic venous constriction were observed after the injection of Arfonad, offering support for previous suggestions that histamine is released. On the basis of these results, total peripheral resistance appears to be divisible into three approximately equal parts—nervous tone, myogenic tone, and the resistance offered by the completely relaxed vessels.

In the present work an attempt was made to maintain the resting vasomotor state before resorting to denervation. A combination of minimal amounts of anesthetic agent, approximately normal "cardiac outputs" and a perfusion technic compatible with the survival of both experimental animals and man was used to accomplish this end. Blood pressure did remain constant during the periods of control output. However, when flow was reduced, blood pressure declined with time, except under special circumstances, as after the administration of Arfonad. A similar temporal decrement in vascular resistance has been previously reported by Green et al. in the perfused muscle preparation. This phenomenon was most marked in the presence of an intact central nervous system; however, it persisted after decapitation and pithing, implying that other factors are also involved. The constancy of resistance at reduced flow rates after the injection of Arfonad indicates that this drug not only relaxes the blood vessels but also renders them unresponsive to both metabolic and nervous stimuli. Pressures obtained at zero flow cannot be considered to be absolute values, as they are likewise arbitrarily determined by the interval between occlusion and the time at which the measurement is made.

The pressure flow curves obtained in the whole animal were linear in the presence of vasodilatation and showed convexity to the pressure axis with higher vasomotor tone. These findings are similar to those reported for regional bed perfusions. The constant presence of a positive pressure intercept at zero flow in these curvilinear relationships makes Green's formula \( F = cP^n \) inapplicable.

The actual mechanism responsible for the presence of a positive pressure intercept has received considerable attention. This phenomenon was originally ascribed to the effects of anomalous viscosity as it did not appear to be
present when saline solutions were used to perfuse the hind limb of the dog. Recent studies in the frog hind limb, rat hindquarter, and perfused rat liver with Newtonian perfusates have consistently demonstrated a finite pressure at zero flow, indicating that this result need not be ascribed to some peculiarity of the perfusing medium, but more probably reflects alterations in vascular dimensions.

Our results indicate that there seems to be a finite pressure intercept at zero flow. However, its magnitude is determined by the length of time at which zero flow exists. This general decay at low pressure indicates that resistance, although high, remains finite and some blood flow continues through the arterioles. It is admittedly impossible in the "intact" animal to determine whether such a high vascular resistance represents a combination of both open and closed vessels or a generalized uniform narrowing of the arterioles. Proof as to whether or not abrupt and complete anatomic closure of the arterioles actually occurs, as has been suggested by Burton and his colleagues, must await more direct technics for studying the response of small vessels to reduced intraluminal tension.

**SUMMARY**

The effect of changes in vasomotor tone on calculated total peripheral resistance was studied in 33 dogs perfused with a pump oxygenator system. Flow rate was maintained constant in these experiments and alterations in vascular tone were induced by surgical decapitation with pithing of the spinal cord or the administration of hexamethonium chloride, trimethaphan camphorsulfonate (Arfonad) and metaraminol (Aramine). Pressure-flow relationships over a wide range of flow rates were determined in 12 of these animals in the "intact" state and in 6 animals after varying changes in vasomotor tone.

The results showed that under the conditions of these experiments, total peripheral resistance in the intact state is made up of three components of approximately equal magnitude. Nervous influences account for one third, inherent myogenic tone in the blood vessels contributes another third and the remainder results from viscous properties of blood and dimensional considerations in the completely relaxed vessels. The vasomotor effects of hexamethonium administration were found to be identical to those following surgical destruction of the central nervous system. Arfonad consistently reduced total peripheral resistance in the completely denervated preparation perhaps as a result of the release of a histamine-like substance.

The pressure flow curves obtained in this study were similar to those previously reported for isolated beds. A positive pressure at zero flow was a uniform finding however its magnitude was arbitrarily determined by the interval between circulatory occlusion and time of pressure measurement. Increased vasomotor tone was associated with a curvilinear pressure-flow relationship convex to the pressure axis while vasodilatation was characterized by a more linear plot. The finding of an infinite resistance at zero flow has been discussed in relation to the concept of critical closing pressures.

**Acknowledgment**

The support given to this work by Dr. C. Walton Lillehei, Professor of Surgery, University of Minnesota Medical School, is gratefully acknowledged.

**Summario in Interlingua**

Le effecto que alterationes in le tono vasomotori exerce super le calculate resistentia peripheric total esseva studiate in 33 canes subjicite a perfusion per medio de un systema oxygenatori a pumpa. Le fluxo esseva mante-nite constante in iste experimentos, e altera-tiones in le tono vascular esseva inducte per decapitation chirurgic con destruction del medulla spinal o per le administration de chloruro de hexamethonium, trimethaphano-camphorsulfonato (Arfonad), e metaraminol (Aramina). Le relation de pression a fluxo, con un extense scala de valores del fluxo, esseva determinate in 12 del animalis in stato intacte e in 6 animales post effectuation de varie alter-terationes del tono vasomotori.

Le resultatos indicava que sub le conditiones de iste experimentos, le resistentia peripheric total in stato intacte es determinate per tres componentes de approximativamente equal
magnitudes. Influences nervous es responsa-
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in le vasos sanguine contribute un secunde
tertio; e le ultime tertio resulta ab le qualitate
viscose del sanguine e ab consideraciones di-

dimensional in le vasos in stato completamente
relaxate. Esse trovate que le effectos vaso-
motori del administration de hexamethonium
esseva identic a illos resultante del destruction
chirurgic del systema nervose central. Esse
note que Arfonad effectuava regulamente
un reduction del resistentia peripheric total
sub conditiones de enervation complete, forsan
como resultato del liberation de un substantia
histaminoide.

Le curvas de pression e fluxo obtenite in iste
studio esseva simile a tal curvas previemente
reportate pro vasculaturas isolate. Un pression
positive al puncto zero del fluxo esseva un
constatation regular. Su magnitude esseva de-
terminate arbitrarimente per le intervallo
inter le occlusion circulatori e le tempore del
mesuration del pression. Augmento del tono
vasomotori esseva associate con un relation de
pression a fluxo que se exprimeva in un curva
da concavitate verso le axe del pression, durante
que le conditiones de vasodilatation resultava
in un curva plus tosto rectilinee. Le constata-
tion de un resistentia infinite con fluxo de valor
zero es discutite in relation al concepto de
critic pressiones de clausion.

REFERENCES
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